



NATIONAL **FRAGILE X** FOUNDATION

Consensus of the Fragile X Clinical &
Research Consortium

MOSAICISM IN FRAGILE X SYNDROME

Published: October 2022



Definitions:

Fragile X gene: Fragile X Messenger Ribonucleoprotein 1 gene, abbreviated FMR1.

Fragile X protein: Fragile X Messenger Ribonucleoprotein 1 protein, abbreviated FMRP, the protein produced by the FMR1 gene.

Methylation: Process which turns the FMR1 gene off, so it cannot make FMRP.

Introduction

This document addresses mosaicism in Fragile X syndrome (FXS), though it should be noted that mosaicism is observed in many genetic conditions. In FXS, both size and methylation mosaicism are seen. Size mosaicism is defined as having both premutation and full mutation repeat expansions in the FMR1 gene. In methylation mosaicism, some cells are methylated, and some are not, resulting in the production of some (varying amounts of) FMRP.

FXS is a genetic condition that can cause learning disabilities, developmental delays, and social and behavioral issues. Significant anxiety is also very common in FXS. Although FXS occurs in both genders, males are more frequently and typically more severely affected than females. FXS is the most common cause of inherited intellectual and developmental disability and the most common known single gene cause of autism spectrum disorder (ASD).

FXS is caused by a DNA expansion in the FMR1 gene, which is located on the X chromosome. The *FMR1* gene includes a repeated DNA code, commonly referred to as “CGG repeats,” as it is composed of DNA elements called cytosine-guanine-guanine (CGG). Most everyone has the FMR1 gene as well as these CGG repeats and typically there are up to 45 CGG repeats, with people in the general population commonly having around 30 CGG repeats. Some people have a small expansion in the gene, with a range of 45–54 CGG repeats, which is also known as an intermediate or gray zone expansion. Individuals with larger expansions may have a premutation (55–200 CGG repeats) or a full mutation (more than 200 CGG repeats). Most people with *FMR1* full mutations show symptoms of FXS.

When the *FMR1* gene has >200 CGG repeats (full mutation), a process called methylation occurs which turns the gene off so it cannot make its protein product, FMRP, and thus results in decreased or absent FMRP; it is FMRP that is needed for typical brain development and functioning. Symptoms of FXS are typically caused by the absence of FMRP due to complete methylation of the *FMR1* gene when there is a full mutation present.

Mosaicism

Mosaicism is a term describing two or more genetic results in the same individual and mosaicism may result in variability in symptoms. In FXS, there are two types of mosaicism:

- Size mosaicism: the most common type of mosaicism in FXS, indicating one or more different “CGG repeat numbers” in the same individual, such that some CGG repeats are in the normal or premutation range and others CGG repeats are in the full mutation range.
- Methylation mosaicism: indicates a pattern where some cells have a methylated *FMR1* gene, which is therefore turned off (no FMRP being produced) while other cells in the same individual have an unmethylated *FMR1* gene, which is still able to make FMRP. This pattern may also be called “partially methylated” when present.

Size Mosaicism

Because of the instability of the CGG repeat when passed down from one generation to the next generation, an individual can have both cells that have CGG repeats in the typical, intermediate or premutation range, while the remaining cells have CGG repeats in the full mutation range. This situation is termed size mosaicism. Since FMRP is typically produced when there is a typical, intermediate, or premutation CGG repeat size, FMRP levels in individuals with size mosaicism may be higher than in individuals with only a full mutation CGG repeat. Size mosaicism may contribute to variable symptoms in these individuals.

Methylation Mosaicism

The process of *FMR1* silencing through gene methylation may not occur equally in all cells. This situation is the basis for a second type of *FMR1* mosaicism: methylation mosaicism, in which those with the full mutation may produce FMRP in a variable proportion of cells.

Both size mosaicism and methylation mosaicism can be present, but regardless of mosaicism status, individuals with an *FMR1* full mutation will almost always show a reduction in typical FMRP level, with wide variability in symptoms.

Does my child have mosaicism?

For Fragile X, there can be mosaicism for different sizes of CGG repeats or different levels of methylation. Most testing laboratories are able to detect significant mosaicism as part of Fragile X DNA testing but will only note it on the lab report when present. If a lab report makes no mention of it, then the lab most likely did not find mosaicism. In any case, it's important that you review your child's Fragile X lab report with a genetic counselor or other qualified healthcare professional who can best interpret the meaning of the results and confirm what type of testing was completed.

Outcomes

As a group, people with mosaicism tend to be higher functioning with fewer symptoms. However, this cannot be predicted on an individual basis. The degree of size and/or methylation mosaicism detected in blood does not necessarily reflect the pattern of mosaicism in the brain or other body tissues.

A recent report from the NFXF's multi-year, multi-clinic, CDC-funded FORWARD study showed that methylation mosaicism is associated with better cognitive functioning and adaptive behavior (less significant developmental delay) and less social impairment relative to the fully methylated full mutation. In contrast, the presence of size mosaicism was not significantly associated with better cognitive and behavioral outcomes than full mutation.

More research needs to be done, but knowing more about how FXS differs in people with and without size and methylation mosaicism may eventually help guide expectations and treatment of individuals with FXS. For now, the general educational and therapy recommendations made for individuals with a full mutation of FXS apply to those with mosaicism, but consideration should be given to the specific needs and functioning of the individual.

For more information:

Fragile X Genetics – Mosaicism

<https://www.youtube.com/watch?v=I4UU2zDH68k>

Genetic Testing for Fragile X Syndrome and Associated Disorders

<https://fragilex.org/understanding-fragile-x/fragile-x-101/testing-diagnosis/>

Mosaicism in Males with Fragile X Syndrome

<https://fragilex.org/research/forward/mosaicism-functioning-males-fxs/>

The association between mosaicism type and cognitive and behavioral functioning among males with fragile X syndrome

<https://pubmed.ncbi.nlm.nih.gov/35148024/>

Size and methylation mosaicism in males with Fragile X syndrome

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5924764/>

Authors' notes: This document was created by Jayne Dixon Weber with assistance from Robert Miller and Brenda Finucane. It has been reviewed by the members of the Fragile X Clinical & Research Consortium.

The **Fragile X Clinical & Research Consortium** was founded in 2006 and exists to improve the delivery of clinical services to families impacted by any Fragile X-associated Disorder and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Please contact the National Fragile X Foundation for more information. (800-688-8765 or fragilex.org)